# EXHIBIT 7

# Long Term Survival of Ovarian Endometriosis Associated Clear Cell and Endometrioid Ovarian Cancers

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**Objective:** This study aimed to analyze long-term survival of clear cells (CCs) and endometrioid (E) ovarian cancer cases according to presence of endometriosis in the pathologic report.
**Methods:** This is a retrospective analysis of 47 CC and 66 E ovarian cancer cases observed consecutively at our center between 1990 and 2010.
All cases had first surgery at our center or were referred to it for treatment and follow-up. Cases were identified according to the original diagnosis reported in clinical records.
All pathologic reports were reviewed, and cases were classified with or without pathologic evidence of endometriosis on the basis of the pathologic report.
Follow-up was updated in March 2011. The follow-up median was 147 months (range, 116–171).
**Results:** Endometriosis-associated ovarian cancer cases were more frequently diagnosed at stage I to II than cases without endometriosis: among the 36 endometriosis-associated ovarian cancer cases, 25 (69%) were at stage I or II, and the corresponding value was 35 (46%) of 77 among cases without endometriosis ($P = 0.0173$).
The presence of endometriosis tended to be associated with a higher 10-year survival rate: after taking the potential confounding effect of stage into account, the finding was not statistically significant (hazards ratio, 0.7; 95% confidence interval, 0.3–1.5).
**Conclusions:** This analysis shows that EA CCs and E ovarian cases are diagnosed at an earlier stage than cases without endometriosis. No clear association emerged between presence of endometriosis and survival.

**Key Words:** Endometriosis, Ovarian cancer, Survival

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In the recent years, attention has been paid to the relation between endometriosis and ovarian cancer.

Clinical and epidemiologic studies have shown that endometriosis is associated with a 2- to 5-fold increased risk of ovarian cancer.[1–3] The ovarian cancer histotypes related with endometriosis are clear cells (CCs) and endometrioid (E) ones.

Furthermore, it has been shown that endometriosis-associated ovarian cancer (EAOC) is diagnosed in younger women and at an earlier stage than in cases without endometriosis.[4]

Whether endometriosis represents a prognostic factor in patients with CC or E ovarian cancer is less clear.[5]

In this study, we have analyzed long-term survival of CC and E ovarian cancer cases according to presence of endometriosis in the pathologic report.

## METHODS

This is a retrospective analysis of 47 CCs and 66 E ovarian cancer cases consecutively observed at our center between 1990 and 2010.

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All cases had first surgery at our center or were referred at our center after surgery for complementary treatment and follow-up.

Cases were identified according to the original diagnosis reported in clinical records.

Data for age, stage at diagnosis, histotype, data of histologic diagnosis, disease status at last follow-up visit, or death were obtained.

All cases underwent total laparohisterectomy and bilateral oophorectomy plus total or partial omentectomy in addition to random biopsies and lymph node dissection for staging procedures when appropriate.

All pathologic reports were reviewed, and cases were classified with or without pathologic evidence of endometriosis on the basis of the pathologic reports.

Stage was defined according to the criteria given by the International Federation of Gynaecology and Obstetrics (FIGO).

Follow-up was updated in March 2011. The follow-up median was 147 months (range, 116–171 months).

## Statistical Analysis

Characteristics of the groups defined by presence of endometriosis were compared using the Pearson $\chi^2$ test or the Fisher's exact test as required.

Patient survival was calculated from the date of histologic diagnosis. Survival probabilities and 95% confidence interval (CI) were estimated using Kaplan-Meier method, and data from the 2 groups were compared using a log-rank test.

Finally, to account for the effect of potential confounding factors simultaneously, we used the Cox regression model (after checking the proportional hazards assumption) to obtain the hazards ratio (HR) and their corresponding 95% CIs.

# RESULTS

Table 1 shows the distribution of study subjects according to the endometriosis diagnosis and selected characteristics.

Endometriosis-associated ovarian cancer cases were diagnosed more frequently at stage I to II than cases without endometriosis: among the 36 EAOC cases, 25 (69%) were at

**TABLE 1.** Characteristics of study subjects

| | | Endometriosis | |
|---|---|---|---|
| | No (n = 77), n (%*) | Yes (n = 36), n (%*) | *P* ($\chi^2$) |
| Age, y | | | |
| 29–39 | 7 (9.1) | 4 (11.1) | 0.3077 |
| 40–49 | 18 (23.4) | 10 (27.8) | |
| 50–59 | 24 (31.2) | 16 (44.4) | |
| 60–69 | 21 (27.3) | 5 (13.9) | |
| 70+ | 7 (9.1) | 1 (2.8) | |
| Mean (SD; range) | 54.3 (11.2; 29–74) | 51.4 (9.8; 29–70) | |
| Stage | | | |
| I–II | 35 (45.5) | 25 (69.4) | 0.0173 |
| III–IV | 42 (54.6) | 11 (30.6) | |
| Histotype | | | |
| CC | 28 (36.4) | 19 (52.8) | 0.0991 |
| E | 49 (63.6) | 17 (47.2) | |
| Grading | | | |
| 1 | 4 (5.2) | 7 (19.4) | 0.1039† |
| 2 | 24 (31.2) | 9 (25.0) | |
| 3 | 47 (61.0) | 20 (55.6) | |
| 4 | 2 (2.6) | 0 (—) | |
| Adjuvant therapy | | | |
| No | 18 (24.0) | 8 (22.2) | 0.8360 |
| Yes | 57 (76.0) | 28 (77.8) | |
| Calendar period at diagnosis | | | |
| 1990–1999 | 57 (74.0) | 21 (58.3) | 0.0928 |
| 2000–2010 | 20 (26.0) | 15 (41.7) | |

*Row percent.
†Fisher's exact test.

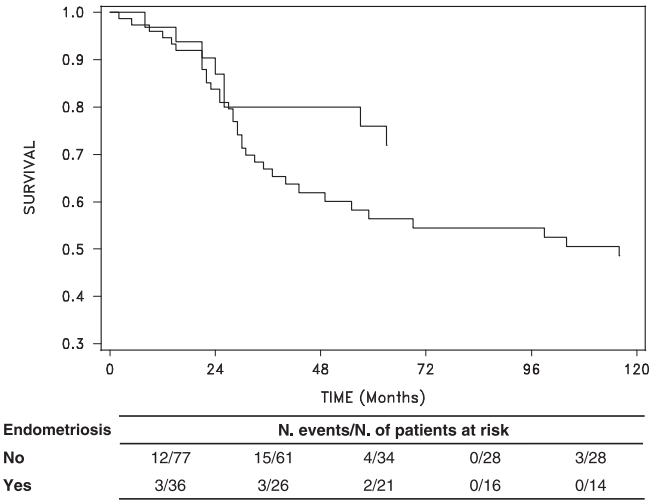


**FIGURE 1.** Ten-year survival in ovarian cancer cases with and without endometriosis.

stage I or II, and the corresponding value was 35 (46%) of 77 among cases without endometriosis ($P = 0.0173$).

Endometriosis-associated ovarian cancer cases tended to be younger than cases without endometriosis, but the difference was not statistically significant ($P = 0.3077$). Likewise, EAOC cases were diagnosed more frequently among CC cases than endometrioid ones, but the finding was not statistically significant ($P = 0.0991$).

The prevalence of endometriosis among ovarian cancer cases was not related with calendar year of first diagnosis of ovarian cancer ($P = 0.0928$).

The presence of endometriosis tended to be associated with a higher 10-year survival rate (Fig. 1, Table 2). After taking the potential confounding effect of stage into account, the finding was not statistically significant (HR, 0.7; 95% CI, 0.3–1.5).

We have analyzed the overall survival further in cases with and without endometriosis in strata of selected characteristics (Table 2). The presence of endometriosis was associated with higher 10-year overall survival (OS) rates in E ovarian cancer cases (HR, 0.2; 95% CI, 0.3–1.4). In particular, the 10-year OS was 100% among women with E ovarian

**TABLE 2.** Ten-year survival in EAOC and not EAOC CCs and E ovarian cancer cases

| | Endometriosis | | Cox Regression* | |
|---|---|---|---|---|
| | No (34 Events) 10-Year Survival, % | Yes (8 Events) 10-Year Survival, % | HR (95%CI) | *P* |
| Age, y | | | | |
| 29–53 | 52.7 (33–69) | 57.7 (26–80) | 1.02 (0.4–2.9)† | 0.9763 |
| 54–75 | 44.7 (28–60) | 82.4 (55–94) | 0.48 (0.1–1.7) | 0.2450 |
| Stage | | | | |
| I–II | 72.1 (51–85) | 84.2 (58–95) | 0.55 (0.1–2.1) | 0.3782 |
| III–IV | 29.5 (15–45) | 44.4 (14–72) | 0.80 (0.3–2.1) | 0.6490 |
| Histotype | | | | |
| CC | | | | |
| Total | 46.4 (26–65) | 57.3 (30–77) | 0.96 (0.4–2.5)† | 0.9337 |
| Grading 1–2 | 50.0 (11–80) | 50.0 (6–84) | 1.35 (0.2–8.8)† | 0.7559 |
| Grading 3–4 | 44.1 (21–65) | 59.1 (27–81) | 0.91 (0.3–2.7)† | 0.8657 |
| Endometrioid | | | | |
| Total | 48.9 (32–64) | 91.7 (54–99) | 0.19 (0.03–1.4)† | 0.1079 |
| Grading 1–2 | 50.8 (23–73) | 100.0 | — | — |
| Grading 3–4 | 47.9 (27–66) | 75.0 (13–96) | 0.41 (0.1–3.1)† | 0.3875 |
| Grading | | | | |
| 1–2 | 52.7 (30–71) | 83.3 (48–96) | 0.50 (0.1–2.3)† | 0.3531 |
| 3–4 | 46.8 (31–61) | 63.4 (35–82) | 0.85 (0.3–2.1)† | 0.7222 |
| Calendar period at diagnosis | | | | |
| 1990–1999 | 45.9 (32–59) | 65.3 (41–82) | 0.57 (0.3–1.3) | 0.1856 |
| 2000–2009 | 70.4 (41–87) | 90.9 (51–99) | 0.36 (0.04–3.1) | 0.3525 |
| Total | 48.5 (36–60) | 72.0 (51–85) | 0.69 (0.3–1.5) | 0.3587 |

*Cox regression for each item (10 years).
†Adjusted for stage.

cancer grade 1 to 2 and endometriosis, but this estimate was based on 12 cases.

## DISCUSSION

This study's results show that EAOC CC and E cases tended to have a better long-term survival than non-EAOC CCs and E ones. In particular, the 10-year OS was approximately 90% among women with E ovarian cancer and endometriosis, but this estimate was based on 17 cases.

The favorable prognostic role of endometriosis was, however, largely explained by the different stage distribution between the 2 groups: early stages being significantly more common among EAOC cases than among those without endometriosis.

Potential limitation of this analysis should be considered. First, this is a retrospective analysis, and data were obtained by clinical records; thus, only hard information, such as age and stage of the disease, were collected. The considered cases were observed during 20 years. During this long period, treatment protocols changed. Likewise, the pathologic criteria may change overtime. In particular, the attention given to the diagnosis of endometriosis in ovarian cancer cases may be changed. The frequency of EAOC cases did not increase among CC and E cases during the study period. Furthermore, the clinical and pathologic staff was largely unchanged over the considered period.

Another limitation of this study is that we were not able to identify ovarian cancer cases in which the cancer was arising in endometriosis and cases in which endometriosis was incidentally found in the surgical specimen, but not in continuity with the tumor.

Endometriosis was diagnosed in 53% of CC ovarian cancer cases and 47% of E ones. These findings are largely consistent with published data.[6–14] For example, in a study that included 221 endometrial epithelial ovarian cancer cases, endometriosis was identified in 82 (37.1%).[6] Similar estimates were reported in other studies.[7–9]

Endometriosis-associated ovarian cancer cases have been suggested to be diagnosed at an early stage. For example, a case control study including 58 EAOC patients and 234 age-matched non-EAOC patients conducted in Slovenia showed that EAOC cases had a statistically significant lower-stage disease (both FIGO and TNM).[4] Similar findings have been reported in other studies.[5,15] A greater proportion of stage I among EAOC cases has been observed in the present study.

It has been suggested that the lower stage at diagnosis in ovarian cancer cases with endometriosis is due to the presence of endometriosis, and its symptoms may cause early diagnosis of the diseases.[16] However, Orezzoli et al (2008)[5] have shown that most patients with EAOC had cancer-related symptoms. Otherwise, it is conceivable that ovarian cancer case arising on endometriosis may have a more benign profile.

Younger age has also been associated with diagnosis of EAOC cases. In the study conducted by Orezzoli et al (2008),[5] patients with CC carcinoma arising in endometrioisis were 10 years younger than those with CC cancer not arising in endometriosis ($P < 0.05$). In our series, cases with endometriosis were, on average, 3 years younger than those without endometriosis, but the finding was not statistically significant.

The role of endometriosis ovarian cancer prognosis is unclear in the literature. Published studies have generally showed that patients with EAOC had higher survival rates, but in most series, this finding was explained by the higher proportion of early stages among ovarian cancer cases with endometriosis.[4,5]

For example, in the previously quoted study by Erzen et al[4] (2001), patients with EAOC showed a significantly better overall survival. This better survival was evident in all age groups and histologic subtypes but not in any FIGO stage.

Orezzoli et al[5] have recently analyzed the role of the presence of endometriosis as a prognostic factor in 84 patients with CC carcinoma of the ovary. In that study, endometriosis was diagnosed in 49% of cases: in 18%, cancer arose in endometriosis, and in 31%, endometriosis was found elsewhere in the specimen. The median OS for patients with endometriosis was 196 months versus 34 months in those without endometriosis. In the interpretation of this finding, the authors underlined that it is possible that the effect on survival associated with the presence of endometriosis might reflect primarily the strong relation between the presence of endometriosis and stage at diagnosis.[5]

Modesitt et al,[15] however, did not find any difference in survival among cases with and without endometriosis.

In our study, overall 5-year survival rate in early-stage cases tended to be higher in women with endometriosis (HR, 0.4; 95% CI, 0.1–2.0). The finding, however, was not statistically significant.

In biological terms, it has been shown[17] that ARID1A (AT-rich interactive domain-containing protein 1A) mutations is common in ovarian CC carcinomas, E carcinomas, but not in high-grade serous ovarian carcinomas. In particular, the loss of the BAF250a protein has been shown strongly associated with the ovarian CC carcinoma and E carcinoma subtypes and the presence of ARID1A mutations. Interestingly, these mutations have been observed in contiguous atypical endometriotic lesions, but not in distant endometriotic lesions far from the carcinoma. Furthermore, in the E ovarian cancers, breast cancer gene inactivation has not been reported.[18]

In conclusion, this analysis shows that EA CC and E ovarian cancer cases are diagnosed at an earlier stage than cases without endometriosis.

No clear association emerged between presence of endometriosis and survival: EA CC and E ovarian cancer cases tended to have a more favorable prognosis, but this finding was at least in part explained by the higher proportion of stage I and II cases in this group.

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